DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

S1797d

TRANSMITTED BY FACSIMILE

JP Garnier, PhD
Chief Executive Officer
GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

RE: NDA # 20-297
Coreg (carvedilol) Tablets
MACMIS ID # 12751

WARNING LETTER

Dear Dr. Garnier:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a convention panel (CRG905ROA) ("panel") for Coreg (carvedilol) Tablets® submitted by GlaxoSmithKline (GSK) under cover of Form FDA 2253 and displayed as a stand alone panel at the 2004 American Society of Health-System Pharmacists (ASHP) conference held June 19-23, 2004, Las Vegas, Nevada. The panel is false or misleading because it omits material risk information and overstates the efficacy of Coreg, and thus misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a), (n) and 321(n), and FDA implementing regulations. This panel raises serious public health and safety concerns because it fails to include any risk information about Coreg, which is associated with serious risks.

Moreover, DDMAC had previously objected, in untitled letters dated October 15, 1997 and February 9, 1999, to your dissemination of Coreg journal advertisements that failed to adequately present risk information. We are concerned that you are continuing to promote Coreg in a similarly violative manner.

Background

According to the Indications and Usage section of the approved product labeling (PI), Coreg is indicated for the following:

> **Congestive Heart Failure:** COREG is indicated for the treatment of mild to severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitor, and digitalis, to increase survival and, also, to reduce the risk of hospitalization (see CLINICAL TRIALS).
>
> **Left Ventricular Dysfunction Following Myocardial Infarction:** COREG is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase

of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure) (see CLINICAL TRIALS).

Hypertension: COREG is also indicated for the management of essential hypertension. It can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics (see PRECAUTIONS, Drug Interactions).

The PI for Coreg contains the following Contraindications:

COREG is contraindicated in patients with bronchial asthma (two cases of death from status asthmaticus have been reported in patients receiving single doses of COREG) or related bronchospastic conditions, second- or third-degree AV block, sick sinus syndrome or severe bradycardia (unless a permanent pacemaker is in place), or in patients with cardiogenic shock or who have decompensated heart failure requiring the use of intravenous inotropic therapy. Such patients should first be weaned from intravenous therapy before initiating COREG.

Use of COREG in patients with clinically manifest hepatic impairment is not recommended.

The Warnings section of the PI contains additional serious risk information, some of which is in the form of bolded warnings:

Cessation of Therapy with COREG: Patients with coronary artery disease, who are being treated with COREG, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with β-blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other β-blockers, when discontinuation of COREG is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. COREG should be discontinued over 1 to 2 weeks whenever possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that COREG be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue COREG therapy abruptly even in patients treated only for hypertension or heart failure (See DOSAGE AND ADMINISTRATION).

Peripheral Vascular Disease: β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Anesthesia and Major Surgery: If treatment with COREG is to be continued perioperatively, particular care should be taken when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. See OVERDOSAGE for information on treatment of bradycardia and hypertension.

Diabetes and Hypoglycemia: In general, β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents,

should be cautioned about these possibilities. In congestive heart failure patients, there is a risk of worsening hyperglycemia (see PRECAUTIONS).

Thyrotoxicosis: β-adrenergic blockade may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate thyroid storm.

Coreg is associated with other risks described in the Adverse Reactions section of the PI. For example, the most commonly reported adverse events in heart failure and Post-MI LVD were bradycardia, hypotension, and dizziness. Additional adverse events reported in >3% of the patients and more commonly on carvedilol were dyspnea, anemia, and lung edema.

Omission of Risk Information

The panel includes the following claims of benefit for Coreg:

- "Broad-spectrum blockade, proven cardioprotection"
- "COREG reduces mortality in Post-MI LVD and in mild to severe HF"
- "COREG provides broad-spectrum blockade, proven cardioprotection"

followed by a graphic presentation depicting efficacy data from the CAPRICORN trial, US CARVEDILOL TRIALS, and the COPERNICUS trial in patients with post-MI LVD, mild heart failure, and severe heart failure, respectively. In addition, the panel presents the indications and uses for Coreg. However, the panel fails to include any risk information (i.e. contraindications, warnings, precautions, or adverse reactions) that is critical to the appropriate use of Coreg. Instead, the reader is advised to actively search out a separate source for the risk information. The reader is directed by the small reference at the bottom of the panel to "Please see complete Prescribing Information available at this exhibit." This isolated reference to seek out risk information does not mitigate the complete omission of risk information in the promotional panel. Moreover, the PI was not readily available for attendees to pick up at the exhibit booth. As described above, the Coreg therapeutic regimen is associated with many serious and significant risks. Omission of any mention of those associated risks raises serious public health and safety concerns.

Overstatement of Efficacy

The panel includes the large bolded header "Broad-spectrum blockade, proven cardioprotection" followed by a graphic presentation that includes the following conditions:

"**Hypertension**
• CAD [Coronary Artery Disease]
• Previous MI [Myocardial Infarction]
• Diabetes"

Because this graphic is presented in conjunction with the header above and the presentation of reduction of mortality and disease progression in specific patient populations (e.g., Post-MI LVD, HF), it appears to suggest that Coreg has demonstrated a cardioprotective benefit in hypertensive patients and specific subsets of hypertensive patients (CAD, previous MI, and diabetes). However, none of the trials (i.e., CAPRICORN, US CARVEDILOL, and COPERNICUS) specifically evaluated

hypertensive patients or specific subsets of hypertensive patients as hypertension was not an inclusion criterion for enrollment in the trials. In addition, FDA is not aware of any studies with Coreg demonstrating cardioprotective benefit in hypertensive patients or specific subsets of hypertensive patients.

Furthermore, the presentation of the relative risk reductions in the CAPRICORN trial, the US CARVEDILOL TRIALS, and the COPERNICUS trial is misleading because it fails to reveal the absolute effect on these events. For example, while the panel shows a 23% relative reduction in mortality in the CAPRICORN trial, the PI states that the actual rates were 15% in the placebo group and 12% in the carvedilol group, a reduction in absolute terms of 3% points (95% CI 2-40%, p=0.03). Inclusion of this important contextual information only in very small type size at the bottom of the panel does not correct the misleading suggestion that Coreg achieved a much greater reduction in mortality than was demonstrated. Similarly, the presentation of relative risk reductions for "Reduction of Disease Progression" in the US CARVEDILOL TRIALS and for "Reduction of Mortality" in the COPERNICUS trial also require necessary context concerning the actual incidence rates of these events.

Moreover, the graphic presentation of the relative risk reduction for "Reduction of Mortality" in the CAPRICORN trial includes the claim "31% in asymptomatic Post-MI LVD patients n=1023." This claim misleadingly suggests that Coreg has demonstrated a 31% reduction in mortality in patients without symptoms of heart failure. However, the subpopulation of Post-MI LVD patients without symptoms of heart failure was not a prespecified subgroup analysis in the CAPRICORN trial. FDA is not aware of substantial evidence or substantial clinical experience to support this claim of benefit in asymptomatic Post-MI LVD patients presented in the panel.

Conclusion and Requested Action

Your panel fails to reveal material facts regarding important risk information for Coreg and overstates the efficacy of Coreg in violation of the Act and implementing regulations, 21 U.S.C. §§ 352(a), (n) and 321(n).

DDMAC requests that GSK immediately cease the dissemination of violative promotional materials for Coreg such as those described above. Please submit a written response to this letter on or before February 14, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Coreg such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8-B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6759. In all future correspondence regarding this matter, please refer to MACMIS ID # 12751 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Coreg comply with each applicable requirement of the Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rebecca Williams
1/31/05 03:52:58 PM
Signed for Thomas W. Abrams